REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 81-96 are canceled without prejudice to or disclaimer of the subject matter therein. Claims 69-80, 97-98, 102, 104, and 106-107 are amended. These amendments are made without prejudice or disclaimer, and Applicant reserves the right to pursue any canceled subject matter in one or more applications with the same rights of priority as the instant application. Claim 108 is added to recite language parallel to that of claim 80. No new matter is added.

Upon entry of these amendments, claims 69-80 and 97-108 will be pending. These claims are presented for reconsideration.

II. Patent Office Interview

Applicant thanks Primary Examiner Kemmerer and Supervisory Examiner Stucker for the courtesies extended during the Patent Office interview on June 12, 2008. Applicant's statement of the substance of the interview is set forth herein.

As noted in the Interview Summary, Applicant discussed the invention, including embodiments relating to altered human IGFBP-2 molecules that exhibit reduced ECM binding and embodiments relating to altered human IGFBP-2 molecules that exhibit resistance to proteolysis. Applicant also discussed the written description and enabling support for the recited embodiments, including enablement of how to use the recited altered human IGFBP-2 molecules in contexts other than the treatment of cancer. Applicant also discussed claim language to overcome the written description rejections, such as language reciting that the altered human IGFBP-2 molecules "differ from a human IGFBP-2 molecule by" recited differences, as adopted in the claim amendments presented above. Applicant also discussed the §101 rejection, and it was agreed that the rejection probably would be withdrawn.

The following remarks build on the topics discussed during the interview, and address the issues raised in the Office Action.

III. Summary of the Invention

As discussed during the interview, Applicant believes that many of the issues raised in the final Office Action stem from an incomplete understanding of the invention. As reflected in independent claim 1, the invention relates to altered human IGFBP-2 molecules that are able to bind IGF-I or IGF-II with high affinity and which differ from human IGFBP-2 by one or more of (i) a substitution of one or more specified lysines and/or (ii) a specified deletion. As noted at page 3 of the specification as filed, the altered IGFBP-2 molecules exhibit inhibited release of IGF-I or IGF-II.

As taught at page 1 of the specification as filed, at least two distinct mechanisms are involved in IGF release from IGFBP: (i) binding of IGFBP to the extracellular matrix (ECM) and (ii) proteolysis of IGFBP. That is, IGFBP releases IGF upon binding to the ECM or upon proteolysis. The altered human IGFBP-2 molecules recited in the instant claims are altered in such a way as to affect one or both of these mechanisms, such that the altered human IGFBP-2 molecules exhibit reduced ECM binding and/or resistance to proteolysis. As taught at pages 4-7 and illustrated in the heparin binding assay reported at pages 23-24, the substitution of one or more of the lysines specified in the instant claims with a neutral or acidic amino acid affects the ECM binding of the altered IGFBP-2 molecule. On the other hand, as taught at pages 7-8 and illustrated in the protease assays reported at pages 21-23, the deletion recited in the instant claims affects the protease resistance of the altered IGFBP-2 molecule. Thus, the recited types of alterations relate to two different mechanisms of IGF release.

The Office Action also notes the conflicting literature on the role of IGFBP-2 in cancer, citing references alleged to show that IGFBP-2 may promote tumor growth. As noted at page 1 of the specification as filed, it is known that IGFPB can either enhance or inhibit IGF action. Inhibition is observed when IGFBP binds IGF, but enhancement occurs when IGFBP releases

IGF. The present invention reduces the risk of the enhancement effect, however, by providing altered IGFBP-2 molecules that exhibit reduced release of IGF.

With this background in mind, Applicant now turns to the issues raised in the final Office Action.

IV. § 101 Rejection

The Office Action rejects claims 69-80 under §101 for allegedly encompassing products of nature. Without acquiescing to the merits of this rejection, Applicant believes that the foregoing amendments obviate this issue. In particular, the claims now recite "altered" IGFBP-2 molecules, thereby reflecting "the hand of man."

V. Enablement Rejections

The Office Action rejects claims 69-72, 74-79, and 97-104 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicant respectfully traverses these rejections for the reasons set forth below.

As noted in MPEP § 2164.01, "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Examples are not required for enablement. *See* MPEP § 2164.02. Moreover, as explained in the MPEP, a claimed genus can be enabled by "representative examples together with a statement applicable to the genus as a whole," as long as "one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." MPEP § 2164.02. In the current application, as noted below, Applicant has sufficiently disclosed the invention to enable the person skilled in the art to make and/or use the invention, as required by §112.

a. IGF binding

Page 6 of the final Office Action questions whether the recited altered IGFBP-2 molecules will bind IGF, noting that working examples were not provided for each altered IGFBP-2 molecule encompassed by the claims. As noted above, working examples are not required for enablement. Moreover, the teachings in the specification provide ample support to enable the claimed altered IGFBP-2 molecules with respect to their ability to bind IGF.

The Examiner appears to acknowledge enablement of embodiments where the lysines at both of positions 180 and 181 have been replaced with alanine, where one of the lysines at positions 227, 234 or 237 have been replaced, or where amino acids 114-170 have been deleted, because these were tested in working examples. Thus, the only issue is whether altered IGFBP-2 molecules with a different amino acid substitution (e.g., a different neutral or acidic residue than used in the examples) or having various permutations and combinations of the illustrated substitutions and deletion will bind IGF. However, the Office Action provides no objective evidence as to why the teachings in the specification are inadequate.

Pages 4 and 7-8 teach regions of the IGFBP-2 molecule that are believed to be important to IGF-binding, and those regions do not coincide with the specified substitutions and deletion. Moreover, the examples show that at least one variation at each of the recited positions did not eliminate IGF-binding. Additionally, the specification discloses a screening assay that can be used to confirm the IGF-binding ability of altered IGFBP-2 molecules. Thus, the record reveals that the skilled artisan will be able to practice the full scope of the claimed invention without an undue amount of experimentation.

Page 6 of the Office Action notes that the single mutants K180A and K181A were not shown to be resistant to proteolysis. This is irrelevant to enablement, however, because the lysine substitutions are designed to affect ECM binding, not proteolsyis, as discussed above.

b. Utility

Pages 6-9 of the final Office Action question enablement of how to use the recited altered IGFBP-2 molecules. At the outset, Applicant strongly disagrees with the assertion at page 6 that because the specification teaches that the recited altered IGFBP-2 molecules may be useful in the treatment of cancer, "predictability of their usefulness in the treatment of cancer has to be evaluated." Because the instant claims are product claims, not method of treatment claims, the enablement requirement is satisfied as long as some practical utility is enabled. That requirement met in several respects.

As taught at page 9 of the specification as filed, the altered IGFBP-2 molecules are useful for decreasing serum or tissue levels of IGF. This utility is supported by the working examples that demonstrate the ability of the altered IGFBP-2 molecules to bind IGF. Moreover, the skilled artisan readily would recognize that the altered IGFBP-2 molecules have utility in *in vitro* applications, such as in binding assays to isolate and purify IGF. Thus, the record shows that the skilled artisan would be able to use the recited altered IGFBP-2 molecules (and corresponding nucleic acid molecules) without any undue amount of experimentation.

The specification also teaches that the altered IGFBP-2 molecules are useful for inhibiting the growth of tumors, as illustrated by data showing, for example, that human IGFBP-2 with the deletion 114-170 reduced proliferation of HT-29 colorectal cancer cells. *See*, e.g., specification at 23-24 & Fig. 6. While the Examiner alleges that the reported data provide support only for the tested altered IGFBP-2 molecule and cell system, Applicant has explained why the skilled artisan would not view the example so narrowly. As set forth in Applicant's previous response, adenocarcinoma HT29 cells are human intestinal epithelial cells which produce the secretory component of Immunoglobulin A (IgA), and carcinoembryonic antigen (CEA). These cells are routinely used in TNF studies as an assay system and as a model of colorectal cancer. Thus, data showing the effect of IGFBP-2 molecules of the present invention on HT-29 cell proliferation

provide general support for the efficacy of the claimed invention in inhibiting proliferation of at least colorectal cancer cells.

For at least the foregoing reasons, Applicant respectfully requests reconsideration and withdrawal of the enablement rejection.

VI. Written Description Rejections

The Office Action, at pages 18-21, rejects claims 69-72, 74, 76-78, 97-100, 102, and 104-106 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicant believes that the foregoing amendments obviate this rejection.

Independent claim 69 now recites "An altered human IGFBP-2 molecule able to bind IGF-I or IGF-II with high affinity, which differs from a human IGFBP-2 molecule by one or more of the following substitutions or deletions: (i) the lysine at one or more of positions 180, 181, 227, 234 and 237 of the human IGFBP-2 molecule has been replaced with a neutral or acidic amino acid; and/or (ii) amino acids 114-170 of the human IGFBP-2 molecule have been deleted." Independent claim 97 recites parallel language. This language was discussed during the Patent Office interview and was proposed by Primary Examiner Kemmerer as likely to overcome the written description rejection. Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

CONCLUSION

Applicant submits that the application is in condition for allowance, and an early notice to that effect is earnestly solicited. Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned directly.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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